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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FULBRIGHT & JAWORSKI LLP
600 Congress Avenue Suite 2400
Austin, TX 78701

EXAMINER
BECKERLEG, ANNE M

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1632	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/526,320	Applicant(s) GABRILOVICH ET AL.
	Examiner Anne M Beckerleg	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31,33-37 and 61-135* is/are pending in the application.

4a) Of the above claim(s) *5-10 and 61-135* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,11-31 and 33-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment and response received on 4/8/02 has been entered. Claims 32 and 38-60 have been canceled. New claims 61-135 have been entered. Claims 1-31, 33-37, and 61-135 are pending in the instant application.

Election/Restriction

The applicant has added new claims 61-135 which do not correspond to the subject matter elected without traverse in paper no.7. The claims as originally filed contained claims drawn to the direct administration of a self-gene to a mammal. In paper no.7, the applicant's elected Group I, claims 1-37, and further elected the species tumor suppressor genes. Applicant's new claims are not drawn to the direct delivery of an expression construct to a subject. Claims 61-135 are drawn to methods of treating a subject with a hyperproliferative disease comprising administering dendritic cells infected *ex vivo* with an expression construct. These claims represent a patentably distinct invention from the elected invention. Expression constructs versus dendritic cells transduced with an expression construct are substantially different in structural, physical, and biological properties, are made using different reagents and methods, and have substantially different modes of operation in vivo. In particular, direct administration of nucleic acids is affected by tropism of the vector encoding the therapeutic gene, the transfection/infection rate of

target cells under *in vivo* conditions, and the rate and duration of gene expression in the target cell, whereas the direct administration of cells transfected with a nucleic acid is affected by the immunogenicity of the implanted cells, the biological properties of the cells themselves, and the level of expression of the heterologous gene product. Thus, the elected invention and the invention of the newly added claims have different modes of operation, and are likely to cause different effects *in vivo* based on the unique properties of nucleic acids versus transfected cells versus protein coated cells. As such, new claims 61-135 are withdrawn from prosecution as being drawn to subject matter non-elected by applicant. As stated in the previous office action, claims 5-10 have also withdrawn from prosecution as being drawn to species non-elected without traverse in paper no.7. Thus, this application contains non-elected claims 5-10 and 61-135. Claims 1-4, 11-31, and 33-37 are currently under examination in the instant application. An action on the merits follows.

Oath/Declaration

The previous office action stated that the oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because: it does not identify the post office address of each inventor. A post office address is an address at which an inventor customarily receives his or her mail and may be either a home or

business address. The post office address should include the ZIP Code designation. The applicant has not complied with this requirement.

Claim Rejections - 35 USC § 112

The rejection of pending claims 1-4, 11-31, and 33-37 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained in a modified form. In view of new grounds of rejection presented below, this office action is non-final. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The scope of enablement has been amended. The instant specification, while being enabling for methods of inhibiting tumor growth of a p53 positive tumor capable of processing and presenting p53 epitopes in the context of MHC on the tumor cell surface comprising intradermal administration of a plasmid DNA encoding p53, does not reasonably provide enablement for treating any type of hyperproliferative disease comprising the intradermal administration of any type of expression construct encoding any tumor suppressor gene.

The applicant argues that the office has not met the legal standard under 35 U.S.C. 112, first paragraph, for the instant finding of non-enablement for the full scope of applicant's invention. The applicant states that case law supports that enablement must bear only a reasonable relationship to the scope of the claims, that the presence of inoperable species does not preclude

enablement of claims. In particular, applicants cite the MPEP and *In re Fisher* for stating that " as long as the specification discloses at least one method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112, is satisfied. In response, it is noted that the previous office action analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of lack of enablement for the scope of the instant methods. The analysis and discussion presented in the previous office action specifically explains why applicant's disclosure does not reasonably correlate with the scope of the claims as written. Furthermore, the applicant is reminded that since, in patentability context, claims are to be given their broadest reasonable interpretations, limitations are not to be read into claims from the specification. *In re Van Guens*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The applicant's claims as amended do in fact recites methods of treating any type of hyperproliferative disease by intradermally administering any type of viral particle comprising an expression construct encoding any self gene. While the applicant has elected the species of tumor suppressor genes for examination in the instant application, the claims have not been amended to reflect the elected species or any tumor suppressor gene in particular. Thus, in analyzing the claims as written, the office properly determined whether the instant specification provides an enabling disclosure for the full scope of

the claims. Also, in regards to inoperative species, the office agrees with the court's conclusions on enablement. Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. "It is not a function of the claims to specifically exclude * * * possible inoperative substances * * * *" *In re Dinh-Nguyen*, 492 F.2d 856, 858-59, 181 USPQ 46, 48 (CCPA 1974) (emphasis omitted). Accord, *In re Geerdes*, 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974); *In re Anderson*, 471 F.2d 1237, 1242, 176 USPQ 331, 334-35 (CCPA 1973). Of course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid. See, e.g., *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971).

In regards to the lack of enablement in the specification for treating any type of cancer comprising the intradermal administration of any tumor suppressor gene, the applicant argues that p53 is overexpressed in roughly 50% of all tumors, and that applicant's have demonstrated the efficacy of p53 therapy in treating tumors. Applicant's arguments regarding p53 are confusing in that the previous office action on page clearly stated that the specification was enabling for methods of inhibiting tumor growth of a p53 positive tumor capable of processing and presenting p53 epitopes in the context of MHC on the tumor cell surface comprising intradermal administration of a plasmid DNA encoding p53 encoding p53. The point of the discussion in the previous office actions of the teachings of Vogelstein et al. and Restifo et al. is that in view of the heterogeneity of tumor suppressor and oncogene mutations in a particular tumor cell and the

various mechanisms by which tumor cells evade immune responses, the lack of guidance provided by the specification for the treatment of tumors which do not overexpress p53, or which do not express p53 at all, and the breadth of the claims, the skilled artisan would have considered it unpredictable at the time of filing to treat any type of tumor other than a tumor which overexpresses p53 and which is capable of presenting p53 epitopes for T cell recognition by generating immune responses according to the instant methodology to any tumor suppressor gene other than p53.

In regards to applicant's statements regarding the evidence provided by the working examples, it is noted that the working examples provided utilize an *ex vivo* approach involving the administration of dendritic cells transduced ex vivo with an adenovirus encoding p53 either i.p, s.c, or i.v. The applicant's working examples do not utilize the intradermal injection route recited in the instant claims. The prior art of record clearly demonstrates that the route of administration of a viral vector has substantial effects on its ability to generate an immune response against a tumor suppressor gene such as p53 (see Hurpin et al.). Further, the direct administration of a viral vector for the transduction of dendritic cells *in vivo* is affected by the rate of clearance of the vector from the injection site, the tropism of the vector for the target cell, and the rate of cell transduction. Thus, these two methods are not equivalent and a nexus cannot be drawn between applicant's *ex vivo* results and the instant methods of treating hyperproliferative disease by direct intradermal injection of viral particles comprising expression constructs.

The applicant has also provided arguments that the specification is enabling for intradermal administration. The scope of enablement identified in the previous office action and recited above indicates intradermal administration of a plasmid encoding p53 is enabled. Thus, applicant's arguments are in this aspect are moot. In regards to the enablement of intradermal administration of viral vectors versus plasmid vectors according to the instant methods, the applicant cites several post-filing references which have not been made of record or provided for consideration by the examiner. As such, the teachings and relevance of these documents cannot be determined. The applicant has provided Harvey et al. for consideration by the examiner. Harvey et al. teaches the generation of host immune responses to recombinant adenoviral vectors following intradermal administration. These host immune responses are characterized as mild to moderate by the authors and specificity of the immune response for the encoded bacterial antigen versus the adenoviral proteins was not determined. Far from promoting the use of adenoviral vectors for immunizing patients with a self-gene, Harvey et al. is interested in decreasing anti-vector immune responses in order to increase transgene persistence in vivo. Further, Harvey et al. relates that no consensus has been reached in the art as to whether the low levels of anti-viral vector immune responses observed actually lead to the destruction of cells expressing genes encoded by the recombinant vectors. Thus, the teachings of Harvey et al. do not provide the enablement lacking in the instant specification for the direct intradermal administration of viral vectors encoding self-genes for the treatment of hyperproliferative diseases. In addition, please note that the applicants in their response to the rejection of the instant claims under 35 U.S.C. 103 have stated that based

on the teachings of Hurpin et al. that intradermal administration of a vaccinia viral vector encoding p53 does not lead to therapeutic anti-tumor immune responses, "one skilled in the art would not expect success generally, much less success using another virus like adenovirus" (see applicant's response page 16).

In regards to the lack of enablement in the specification for the treatment of any and all hyperproliferative diseases, the applicant argues that p53 has recently been implicated as having a role in rheumatoid arthritis and lichen schlerosus. In support, the applicant has again cited several post-filing references which have not been made of record or provided for consideration by the examiner. As such, the teachings and relevance of these documents cannot be determined. The applicant has provided the cited article by Muller-Lander et al. Muller-Lander teaches that recent evidence may indicate a role for p53 in rheumatoid arthritis. Muller-Lander, however, clearly states that it is not known whether p53 expression in RA synovium is wild type or mutated or whether the expression of p53 is actually involved with the pathophysiology of RA. Further, it is noted that RA is an inflammatory disease where the RA synovium already contains numerous immune effector cells which are apparently not activated against p53. Ultimately, Muller-Lander et al. provides no suggestion or specific teaching that immune responses can be generated against p53 or that any such immune responses would in fact be capable of treating RA. Furthermore, in regards to post-filing references, please note that as stated in In re Glass, 181 USPQ 31, (CCPA 1974), if a disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while the application is still pending by later publications which add to the knowledge of the art so that the

disclosure, supplemented by such publications, would suffice to enable the practice of the invention. Instead, sufficiency must be judged as of the filing date.

The applicant's claim have been amended to recite that the intradermal administration of a viral particle comprising an expression construct encoding a self-gene results in the expression of the self-gene in dendritic cells. The specification does not provide sufficient guidance for the targeted transduction of dendritic cells following intradermal administration of either viral or non-viral vectors. At the time of filing , the skilled artisan did not consider the targeting of vectors to specific cell types *in vivo* to be predictable . Deonarain, in a review entitled, " Ligand-targeted receptor-mediated vectors for gene delivery", teaches that one of the main obstacles to successful gene therapy is, " ... the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time", and states that, " .. even after almost 30 years of relentless pursuit, nothing has yet delivered such a promise in terms of clinical results" (Deonarain et al. (1998) Exp. Opin. Ther. Patents, Vol. 8 (1), page 53, lines 1-4, and page 54, lines 12-15). Miller et al. concurs, teaching that the development of surface targeting has been problematic and that the biggest challenge in targeted vector design is to combine targeting with efficiency of gene expression, since , " attainment of one usually compromises the other" (Miller et al. (1995) FASEB, Vol. 9, page 198, paragraph 2). The specification does not provide guidance in the form of detailed teachings or specific working examples for methods to target any vector to dendritic cells or any other cell type *in vivo*. Therefore, in view of the art recognized unpredictability in achieving targeted gene delivery *in vivo* using vectors currently available at the

time of filing and the absence of guidance for methods for the targeted transduction of dendritic cells using viral or plasmid vectors *in vivo*, it would have required undue experimentation to practice the instant invention as claimed.

In regards to the lack of enablement for the use of any and all types of expression constructs in the instant methods, the applicant argues that unpredictability is not grounds for non-enablement, it is merely a factor. The courts disagree. In *Ex parte Singh*, it was found that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). However, as stated above, the office has not relied solely on unpredictability in analyzing the instant specification. The specification was analyzed in accordance with all the factors identified in *In re Wands*. Furthermore, contrary to applicant's assertion, FDA standards were not applied to the instant application. In regards to the cited references, Verma et al., Orkin et al., and Marshall et al. teach the unpredictability of achieving therapeutic levels of expression of a transgene in vivo by direct administration of a recombinant vector, including both plasmid vector and viral vectors. The references base their analysis of the state of the art of gene therapy not simply on clinical trial data, but also on data from in vitro studies and in vivo studies in art accepted animal models. Thus, the papers do not rely on any particular standard, FDA or otherwise, but simply review the problems associated with gene therapy using recombinant vectors at the time of filing. As discussed in the previous office action, the combined teachings of Verma et al., Orkin et al., Marshall, and Ledley et al. clearly indicate that at the time of filing, the

skilled artisan did not consider the expression of therapeutically effective amounts of a protein in vivo using plasmid vectors or viral vectors as either routine or predictable. Further, the office has not relied solely on these teachings to establish non-enablement, see above. These references were cited to demonstrate the state of the art of vector therapy at the time of filing and its associated unpredictability. The instant finding for lack of enablement for the full scope of the instant invention was based on the art recognized unpredictability of generating therapeutic levels of gene expression using both viral and non-viral vectors at the time of filing, the art recognized differences in the ability of vectors to generate immune responses to encoded proteins based on the route of administration, the specific teachings of Hurpin et al. that the intradermal injection of vaccinia virus encoding p53 fails to generate p53 immune responses, the lack of working examples in the specification demonstrating the direct administration of any expression construct encoding p53, and the breadth of the claims. Ultimately, case law states that ".. the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970. Based on the lack of guidance provided by the specification for the full scope of applicant's claims, and the lack of reasonable correlation between the subject matter found to be enabled and the breadth of the claims, it would have required undue experimentation to practice the scope of applicant's invention.

Claim Rejections - 35 USC § 102

The rejection of claims 1-4, 11, 20-30, and 33 under 35 U.S.C. 102(b) over Hurpin et al. is withdrawn in view of applicant's amendment to the claims.

Claim Rejections - 35 USC § 103

The rejection of claims 1, 12-19, and 32 under 35 U.S.C. 103(a) over Hurpin et al. in view of Fang et al. and Reed et al. is withdrawn in view of applicant's amendments to the claims and arguments.

The rejection of claims 1 and 34-37 under 35 U.S.C. 103(a) over Hurpin et al. in view of Xiang et al. and Rosenthal et al. is withdrawn in view of applicant's amendments to the claims and arguments.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the

examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé